DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

MAR 23 2005

Office of the Commanding General

U.S. Food and Drug Administration
Division of Dockets Management
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Ladies and Gentlemen:

Reference Docket Number 1980N-0208, Proposed Rule and Proposed Order: Bacterial Vaccines and Toxoids. This comment pertains to Section IV of the Proposed Rule and Proposed Order: Anthrax Vaccine Adsorbed (AVA) – Proposed Order. The commitment of the Food and Drug Administration (FDA) to a prompt completion of this regulatory process is of critical importance to public health and national security given that anthrax spores represent the number one bioterrorism and biowarfare threat against the United States and its Armed Forces.

The focus of this comment is the proposed order's discussion concerning the conclusion of the Institute of Medicine (IOM) regarding the efficacy of anthrax vaccine (IOM 2002; see enclosure for bibliography of cited documents). The FDA's proposed order references the IOM conclusion, but is somewhat indirect in commenting on it (FDA 2004, page 78286). The FDA should accord the IOM report significant weight as expert scientific judgment. Based on the underlying scientific evidence, the FDA should strongly endorse the IOM's conclusion that "the available evidence from studies with humans and animals, coupled with reasonable assumptions of analogy, shows that AVA as licensed, is an effective vaccine for the protection of humans against anthrax, including inhalation anthrax" (IOM 2002, page 77).

The IOM report should be accorded significant weight as an expert opinion for several reasons. First, the IOM review was chartered by the U.S. Congress specifically for the purpose of providing the best possible, comprehensive, independent scientific assessment of anthrax vaccine to resolve questions that had been raised concerning the Department of Defense program (U.S. House of Representatives, 1999). The IOM review process included an internal critique process by a second panel of distinguished experts who provided "candid and critical comments" (IOM 2002, pages xi–xii) before the final report was published. Second, the IOM review was decidedly independent and considered the entire spectrum of views (Larkin 2002). Third, the IOM conclusion reflects the consensus view previously expressed by other prominent

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independent reviews over several years, including the civilian physicians and scientists who serve on the Armed Forces Epidemiological Board (AFEB 1994-2002).

The IOM report's conclusion that "the available evidence from studies with humans and animals, coupled with reasonable assumptions of analogy, shows that AVA as licensed, is an effective vaccine for the protection of humans against anthrax, including inhalation anthrax" is correct. The primary evidence is the Brachman study, a well-controlled, randomized field trial of a comparable predecessor vaccine, supported by at least four elements of corroborating evidence (Brachman et al., 1962). The Brachman study concluded that the calculated efficacy of the vaccine in preventing all forms of anthrax disease combined was 92.5% (95 percent confidence interval = 65% to 100%), including all cases of cutaneous or inhalational exposure in the vaccinated and placebo groups. The conclusion that the assessment of efficacy is applicable regardless of the route of exposure is corroborated by the available evidence.

The first notable element of corroboration is in the observational group of the Brachman study, in which there were three additional cases of inhalation anthrax, all among unvaccinated individuals. Corroborating evidence is also found, as noted by the Panel on Review of Bacterial Vaccines and Toxoids, in the Centers for Disease Control surveillance data covering the period 1962-1974, which identified 27 cases of anthrax disease, none among individuals fully vaccinated. A third source of corroborating evidence is in the collective results of a series of studies of the efficacy of AVA in protecting macaque monkeys, an animal model for which the IOM notes the pathophysiology of anthrax is strikingly similar to that in humans. Overall in these studies, 95% of the vaccinated macaques survived inhalation challenges with dozens to a thousand times the median lethal dose, compared to 100% fatality among unvaccinated macaques. Experimental challenge data in rabbits, another animal model the IOM considers appropriate for studying the human form of inhalation anthrax, are similar. A fourth form of corroboration is in the well-understood pathophysiological mechanism of the anthrax bacteria and the effect at the cellular level of antibodies that bind to the protective antigen (PA) portion of the toxins secreted by the bacteria after entry into the body. These antibodies, produced in response to the protective antigen component of anthrax vaccine, appear to prevent entry into the cell of the lethal factor protein of the toxin, thereby preventing the cellular damage and disease (IOM, 2002, pages 46-48, 72-73).

The IOM committee, Congressionally chartered, selected from America's best university faculty members, strongly independent, peer reviewed before publication, and representative of prevailing expert scientific judgment, produced a well-considered and clearly supported conclusion: the available evidence from studies with humans and animals, coupled with reasonable assumptions of analogy, shows that AVA as licensed, is an effective vaccine for the protection of humans against anthrax, including inhalation anthrax.

My point of contact for this correspondence is Colonel Jerome F. Pierson, Commander, U.S. Army Medical Materiel Development Activity, 301-619-7643, email: jerry.pierson@det.amedd.army.mil.

Sincerely,

Lester Martinez-Lopez, MD, MPH
Major General, Medical Corps
Commanding

Enclosure

Annotated Bibliography

Armed Forces Epidemiological Board (AFEB) recommendations: August 1994, November 1996, April 1998, March 2000, March 2002, www.tricare.osd.mil/afeb/, www.anthrax.mil/resource/library/afeb.asp. See also Cochrane Collaboration, 1998, 2004, Demicheli V, Rivetti D, Deeks JJ, Jefferson T, Pratt M. The effectiveness and safety of vaccines against human anthrax: A systematic review. *Vaccine* 1998;16 (May-Jun):880-4. www.anthrax.mil/media/pdf/EffandSafety.pdf . Updated in 2004: www.cochrane.org/cochrane/revabstr/ab000975.htm Working Group on Civilian Biodefense, Inglesby TV, Henderson DA, Bartlett JG, et al., Anthrax as a biological weapon: Medical and public health management. *Journal of the American Medical Association* 1999;281 (May 12):1735-45. jama.ama-assn.org/cgi/reprint/281/18/1735.pdf ; Inglesby TV, O'Toole T, Henderson DA, et al. Anthrax as a biological weapon, 2002: Updated recommendations for management. *Journal of the American Medical Association* 2002;287 (May 1):2236-52, jama.ama-assn.org/cgi/content/short/287/17/2236; Advisory Committee on Immunization Practices (ACIP), Use of anthrax vaccine in the United States. *Morbidity and Mortality Weekly Report (MMWR)* 2000;49 (RR-15) (Dec 15):1-20, www.cdc.gov/mmwr/PDF/rr/rr4915.pdf.

Brachman PS, Gold H, Plotkin S, Fekety FR, Werrin M, Ingraham NR. Field evaluation of a human anthrax vaccine. *American Journal of Public Health* 1962;52: 632-645. www.anthrax.mil/media/pdf/field_eval.pdf

Food & Drug Administration. Biological products; Bacterial vaccines and toxoids; Implementation of efficacy review; Proposed rule and proposed order. Fed Reg 2004;69(Dec 29):78281-93. www.fda.gov/cber/rules/bvactox.pdf

Institute of Medicine (Joellenbeck LM, Zwanziger LL, Durch JS, Strom BL, eds). *The Anthrax Vaccine: Is it Safe? Does it Work?* Washington, DC: National Academy Press, April 2002. www.nap.edu/catalog/10310.html. Summary for Policy Makers: www.iom.edu/Object.File/Master/4/150/0.pdf. First quote from page 77; the IOM report conclusion goes on to comment concerning plausible engineered strains of the anthrax bacteria, but that issue is outside the scope of the proposed order and this letter.

Larkin M. Anthrax vaccine is safe and effective – but needs improvement. Lancet 2002;359(Mar 16):951. pdf.thelancet.com/pdfdownload?uid=llan.359.9310.news.20380.4&x=x.pdf See also IOM Report, p. 35 and Appendix C. The IOM Committee Chair was quoted as saying: "[I]f we had a bias to begin with, it probably was against the military. I felt we just had to turn over the right stone and we'd find a smoking gun out there. But we didn't find it, and we looked hard."

U.S. House of Representatives, Conference Report 106-371, Conference Report to Accompany H.R. 2561, the proposed Department of Defense Appropriations Act, 2000, October 8, 1999, page 254.